Anesthesiology

FDA Announces Nationwide Recall of Nellcor Puritan Bennett Probes Device

Probe and Associated Saline Found to Contain Bacteria *Burkholderia cepacia*

On August 27, 2004, FDA announced that Nellcor Puritan Bennett (Tyco Healthcare/Mallinckrodt) was conducting a nationwide recall of all of its CapnoProbes, a device similar to an electronic thermometer that is used by hospitals to measure the carbon dioxide in patients' tissues. Each probe is packaged in a metal canister filled with a saline solution and sealed in a foil envelope labeled as non-sterile. All of the CapnoProbes were manufactured at Nellcor's facility in Tijuana, Mexico.

The probe and associated saline contained the bacteria *Burkholderia cepacia* and other opportunistic pathogens that can cause serious infections, usually in persons who have decreased resistance to infection.

FDA first learned of a potential problem with the product when the Agency was notified by the Texas Department of Health on August 18, 2004. Positive cultures were found in at least eleven patients in the pediatric intensive care units of Children's Medical Center in Dallas. An association with these specific culture findings and patient outcomes had not been established at this time. On August 19, FDA sent an investigator to Nellcor's corporate headquarters in Pleasanton, California, to conduct an inspection.

On August 24, 2004, Nellcor notified its customers that they were recalling all lots of the CapnoProbe SLS-1 Sublingual Sensors and asked hospitals to return any unused inventory. The firm said the probe may pose a hazard to patients with compromised immune systems.

FDA Announces Recall of Breathing Circuit Adaptors

Unomedical Inc. is a McAllen, TX, based manufacturer of respiratory and infusion device components. The firm initiated a recall of their 22mm/15mm airway connector on November 30, 2004. The adapter is used as an accessory connector typically used for extending airway circuits and attaching various breathing circuit components.

Several reference numbers of the adapter were found to be occluded due to flash during the injection molding process. FDA first became aware of the problem when Washington State Medical Center reported that 4 connectors from 2 lots were fully occluded by a plastic

membrane. The adapter was being used to connect the reservoir bag for positive pressure ventilation on a child during post-anesthesia recovery. This occluded the exhalation limb and pressurized oxygen was being introduced into the circuit. The child suffered bilateral pneumothoraces, pneumoperitoneum, pneumomediastinum and subcutaneous emphysema in relation to the use of an occluded connector.

CDRH classified the recall as Class I December 3, 2004. The firm issued a nation-wide press release December 2, 2004, providing notification of the problem, what lot numbers are affected, and the subsequent manufacturers using the device as a component. A recall notice was also sent December 2, to all consignees indicating the recall of the adapter. A subsequent recall, also classified as Class I, of Bio-Med Devices, Inc. airway circuits has also been conducted.

Bioresearch Monitoring

Warning Letter Issued to Investigator for Failure to Obtain FDA Approval

Investigator Proceeds to Use Unapproved Investigational Device

On March 25, 2004, the Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) issued a Warning Letter to Mark Reisman, M.D., Director of Cardiovascular Research Department, Swedish Medical Center, Seattle, Washington. FDA conducted an inspection during the period of November 5 - 25, 2003. The purpose of the inspection was to determine whether Dr. Reisman's activities as a sponsor and principal investigator of an investigational study involving significant risk devices complied with applicable FDA regulations. Dr. Reisman used significant risk devices to treat migraine headaches.

The Warning Letter noted that in February 2002, Dr. Reisman submitted an application to FDA for an Investigational Device Exemption (IDE) for the study of the treatment of migraine headaches. This application was disapproved on March 28, 2002, by FDA's Office of Device Evaluation (ODE) in CDRH. In the disapproval letter, ODE stated that the risk of device placement outweighed the potential benefit of the proposed treatment for migraine headaches.

Subsequently, Dr. Reisman applied to his Institutional Review Board (IRB) for approval to conduct his investigational study. The IRB approved the study on December 5, 2002. Dr. Reisman enrolled the first patient on January 21, 2003, almost ten months after ODE had disapproved his IDE application. Between January 21 and September 17, 2003, the

investigational devices were implanted in nine patients at the Swedish Medical Center to treat migraine headaches.

The Warning Letter noted that Dr. Reisman was an experienced clinical investigator and had full knowledge of the disapproval letter from FDA, and therefore was aware that he needed FDA approval before conducting a clinical investigation using the investigational devices to treat migraines.

The Warning Letter cited Dr. Reisman for:

- Failure to obtain FDA approval prior to beginning the study; and
- Failure to obtain adequate informed consent.

Warning Letter Issued to Clinical Investigator for Serious Violations

On March 25, 2004, FDA issued a Warning Letter to Timothy A.M. Chuter, M.D., Division of Vascular Surgery, University of California, San Francisco, California. Investigators from FDA's San Francisco District Office conducted an inspection of Dr. Chuter's clinical site from November 17- December 4, 2003.

FDA conducted the inspection under a program designed to ensure that data and information contained in applications for IDEs, Premarket Approval (PMA) applications, and Premarket Notification (510(k)) submissions are scientifically valid and accurate. Another program objective is to ensure that human subjects are protected from undue hazard or risk during scientific investigations.

FDA's review of the inspection report prepared by the San Francisco District Office revealed serious violations of Title 21, Code of Federal Regulations, Part 812 (21 CFR Part 812), IDEs, and 21 CFR Part 50, Protection of Human Subjects.

The inspection report disclosed the following violations:

- Failure to adequately document informed consent; including required information in the consent document, and failure to maintain signed consent forms for all subjects;
- Failure to prepare and submit complete, accurate, and timely reports;
- Failure to properly monitor the studies and to select qualified monitors;

- Failure to maintain accurate, complete, and current records relating to participation in the study(ies); and

- Failure to adhere to the investigational plans and obtain FDA approval prior to implementing changes in the plans.

Hospital Institutional Review Board Receives Warning Letter

On August 25, 2004, FDA's CDRH issued a Warning Letter to Patrick Farrell, Chief Executive Officer (CEO), Henrico Doctors' Hospital, Richmond, Virginia. An FDA investigator from the Baltimore District Office conducted an inspection at Henrico Doctors' Hospital Institutional Review Board (IRB) from April 6 - 9, 12 - 13, and 20, 2004.

A review of the inspection report prepared by the Baltimore District Office revealed serious violations of 21 CFR Part 56-IRBs. The deviations noted on the List of Inspectional Observations (Form FDA 483) included the following:

- Failure to prepare, maintain, and follow adequate written procedures;
- Failure to assure that the informed consent documents included all of the statements and information that are required in an informed consent;
- Failure to conduct adequate continuing review; and
  Failure to maintain adequate documentation of IRB activities.

Three Firms Placed on Application Integrity Policy List

FDA Investigations Disclose Significant Violations of Human Subject Protection Regulations

The Division of Bioresearch Monitoring in the Office of Compliance invoked FDA's Application Integrity Policy for applications for three firms based upon inspectional findings at the application sponsor and clinical investigator sites. The inspections indicated system-wide and data integrity problems that revealed multiple violations of human subject protection regulations as well as unreliable research data that compromised the integrity of the FDA approval process. As a result of being placed on the Application Integrity Policy List, one firm withdrew six suspect applications and sent registered letters to all patients (mostly elderly) indicating that they had been implanted with investigational orthopedic implants (e.g., hip and knee) without adequate informed consent.

This investigation also resulted in the initiation of disqualification proceedings against at least three clinical investigators associated with the research. At a second firm, FDA stopped the research of a pediatric cardiology device due to failure of the firm to report two pediatric deaths directly associated with the use this device prior to FDA approval of its use in research. Moreover, FDA inspections uncovered information that revealed inadequate sterilization of this implantable device as well as lack of control over its distribution and use. At the third firm, FDA suspended review of a pending application for an infectious disease diagnostic device when an inspection revealed serious data omissions and inconsistencies between source data the clinical sites and data submitted to the Agency.

The Application Integrity Policy is applied to the applications of firms that have engaged in wrongful acts that raise significant questions regarding data reliability in research or marketing applications submitted to FDA for review. Once the Application Integrity Policy is invoked on a firm's application, FDA stops substantive scientific review of all the firm's pending applications and may ask the firm to withdraw any approved or cleared applications that they feel may contain unreliable data. The firm must also go through a lengthy process to satisfactorily demonstrate that they have corrected all violations associated with the lack of human subject protections or submission of unreliable research data. Furthermore, firms must demonstrate that they have implemented additional procedures and controls that will prevent further recurrence of these violations.

Unapproved Pediatric Device Removed from the Market

FDA Investigation Discloses Physicians Implanting Unapproved Device in Infants and Children

Following up on a research misconduct complaint regarding the use of an unapproved pediatric cardiology device, FDA found that several physicians implanted infants and children with this device to treat a specific congenital heart defect. The physicians implanted this device without FDA or an institutional review board's (IRB) approval and without informing the children’s families that they were being treated with an unapproved device or that they were participating in research. While use of the unapproved device may negate the need for open heart surgery in some cases, not all of the clinical outcomes were positive.

The FDA investigation prompted the hospital's IRB to conduct their own internal investigation into these research activities. Two participating doctors and a senior administrator were dismissed from the hospital, and the research was stopped. A follow up inspection at the device manufacturer revealed other physicians who had also been shipped the unapproved device.

Appropriate FDA regulatory and administrative response resulted in an unapproved device being removed from the market and pediatric patients' families being notified that their child had been treated with an unapproved device, and informed who to contact for follow-up.

Further research of this unapproved device will be conducted under a carefully designed, FDA-IRB approved clinical trial.

Cardiovascular

Problems With Coronary Stent Result in Warning Letter

On April 1, 2004, FDA's CDRH issued a Warning Letter to Richard D. Anderson, President, Cordis Cardiology, Cordis Corporation, Miami Lakes, Florida. FDA performed post-approval inspections of Cordis Corporation and its facilities involved in the design, manufacture and distribution of the CYPHER™ Sirolimus-Eluting Coronary Stent. The inspections were performed in September, October and December 2003, at Cordis' facilities located in: Miami Lakes, Florida; San German, Puerto Rico; Warren, New Jersey; Roden, Netherlands; Beerse, Belgium; and Latina, Italy.

The purpose of the Warning Letter was to apprise top management of the observations made at these facilities and to remind Mr. Anderson of his responsibility to assure all facilities are in compliance with the Federal Food, Drug, and Cosmetic Act (the Act) and all pertinent regulations. FDA expressed concern with the breadth and scope of the specific violations noted in the Warning Letter and the inspectional observations noted on the Form FDA 483.

The inspections revealed that CYPHER™ Sirolimus-Eluting Coronary Stents are adulterated in that the methods used in, or the facilities or controls used for, the design, manufacturing, packing, storage, or installation are not in conformance with the Current Good Manufacturing Practice (CGMP) requirements for medical devices which are set forth in the Quality System (QS) Regulation. FDA's inspection found systemic violations in the quality management system employed to ensure the safety and effectiveness of drug-eluting stents that recurred at several facilities. Significant deviations from the QS Regulation included, but were not limited to, the following:

Corrective and Preventive Action Subsystem

- Failure to establish and maintain adequate procedures to control product that does not conform to specified requirements including the identification, documentation, evaluation, segregation, and disposition of nonconforming product, and to review and dispose of nonconforming product, with documented justification for use of nonconforming product because cites weren't included in other sections;

- Failure to establish and maintain adequate procedures for corrective and preventive actions; and

- Failure to establish and maintain adequate complaint handling procedures to ensure all complaints are evaluated and investigated, and processed in a uniform and timely manner.

Production and Process Controls Subsystem

- Failure to validate with a high degree of assurance, processes, including changed processes, that cannot be fully verified by subsequent investigation and test.

Design Control Subsystem

- Failure to establish and maintain adequate procedures for validating the device design to ensure that the device conforms to defined user needs and intended uses and to ensure that design validation is performed under defined operating conditions on initial production units or their equivalents.

FDA stated that the Agency had received and reviewed several responses that Cordis had supplied as a result of Form FDA 483s issued at the above mentioned facilities. FDA acknowledged the general commitments made and the fact that some of the responses to certain Form FDA 483 items appeared to propose adequate corrective actions.

The Warning Letter stated, "However, in general Cordis' responses appear to be specific spot fixes and do not take a systematic approach to comprehensively cover the corrections, the corrective actions and the preventive actions. None of the responses adequately deal with true preventive actions. Further, the responses fail to bring together the corporate corrective and preventive actions necessary to tie the operations of all these facilities together as they all contribute to manufacture this particular product."

Medical Device Service, Inc. Signs Consent Decree of Permanent Injunction

United States v. Medical Device Service, Inc., (D. Utah). On May 18, 2004, U.S. District Court Judge Tena Campbell entered a Consent Decree of Permanent Injunction (decree) against the defendants, medical device reprocessors. Defendants represented in the decree that they have ceased operations and will not

resume manufacturing (including reprocessing), packing, storing, or distributing any articles of device.

If the defendants should resume operations, the decree imposes certain conditions to ensure that future products are manufactured in compliance with the law. The decree provides that FDA may exercise recall authority, and/or recommend that the court apply the arbitrary and capricious standard of review.

Ear, Nose and Throat

FDA Announces Recall of Cochlear Implants

Cochlear Implants Recalled Due to Malfunction Caused by Moisture

On September 24, 2004, FDA announced that Advanced Bionics Corporation, a wholly owned subsidiary of Boston Scientific Corporation, was conducting a voluntary recall of its not yet implanted CLARION and HiResolution cochlear implants because some of the devices may malfunction due to moisture. The firm's recall included notification to doctors and other healthcare professionals and patients.

Cochlear implants are intended to restore a level of auditory sensation to adults and children with severe-to-profound hearing loss via electrical stimulation of the auditory nerve.

Advanced Bionics determined that device failure may occur due to moisture inside the product. Symptoms associated with device failure included, but were not limited to: 1) intermittent functioning; 2) sudden sensation of discomfort or pain; 3) sudden loud noise or popping sound; 4) complete loss of sound; and 5) unwillingness of a child to wear his or her external headpiece.

Patients who experience difficulties with these cochlear implants were advised to try the backup cable, headpiece, and then the sound processor. If signs or symptoms persist, users were advised to remove the headpiece and contact his or her hearing care provider.

General Hospital and Personal Use

Class I Recall of Insulin Administration Sets

On May 6, 2004, the FDA's Center for Devices and Radiological Health classified Medtronic Minimed's voluntary recall of 1,676,546 Paradigm Quick-set Plus insulin administration sets as a Class I recall. Prior to the recall classification, the firm had ceased distribution of further Quick-set Plus sets due to high complaint rates. Minimed began distributing the Quick-set Plus in November 2003 and ceased distribution in March 2004. Reports indicate hospitalizations for high blood glucose following complaints of problems with the Quick-Set Plus, in particular, bent cannulas. Some patients reported multiple incidents of problems before the severe event, which led to hospitalization. Upon classification of the recall, the firm decided to remove any of the devices still in distribution and to give customers replacement sets of a different model at no charge.

Insulin Infusion Pumps on Import Alert

Numerous Violations of the Quality System Regulation Puts Korean Firm on Import Alert

On November 24, 2004, the FDA's Center for Devices and Radiological Health (CDRH) issued a Warning Letter with Detention Without Physical Examination to Sooil Development Co Ltd., an insulin infusion pump manufacturer located in Seoul, Korea. Insulin infusion pumps, a Class II medical device, have been the subject of much scrutiny by CDRH and this is the second firm to have their pumps placed on automatic detention. The first, Disetronic Medical Systems AG, was placed on automatic detention after receiving a Warning Letter on June 10, 2003. The insulin pump is about the size of a pager and is worn on the hip. The insulin is continuously inserted into the diabetic's body through a thin plastic tube called an infusion set. The infusion set is inserted under the skin by a needle or soft cannula, usually in the abdomen. The insulin is delivered continuously (the basal rate), which is set by the user. After meals, the user will program a "bolus" dose of insulin according to what was eaten.

Sooil Development was issued a Warning Letter for the following violations:

- Failure to establish and maintain adequate procedures to control product that does not conform to specified requirements;
- Failure to investigate, and maintain complaint files on complaints involving the possible failure of a device to meet any of its specifications, unless such

investigation has already been performed for a similar complaint and another investigation is not necessary;

- Failure to establish and maintain procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics;

- Failure to evaluate whether there was any adverse effect on product quality after learning that test/measurement equipment was found not to meet its accuracy and precision limits;

- Failure to document the results of the design validation in the design history file;

- Failure to maintain adequate procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation;

- Failure to adequately establish and maintain procedures for implementing corrective and preventive action (CAPA), which include requirements for analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product;

- Failure to document the CAPA activities including investigations of causes of nonconformities and dissemination of information about quality problems or nonconforming product to responsible parties;

- Failure to document the approval, prior to issuance, of documents established to meet the requirements of 21 CFR Part 820;

- Failure to maintain records of changes to documents;

- Failure to document equipment maintenance activities;

- Failure to document acceptance activities;

- Failure to have completed procedures for the acceptance or rejection of finished device production runs; and,

- Failure to maintain adequate procedures for acceptance activities such as inspections, tests, and verification activities.

Destruction of 94 Insulin Infusion Pumps

On November 10, 2004, the FDA's New Orleans District observed the voluntary destruction of 94 Dana Diabecare II Insulin Infusion Pumps due to a firm initiated recall on June 14, 2004. The pumps affected were valued at $470,000.00. The Dana Diabecare II insulin pumps are manufactured by Sooil Development Co Ltd. of Seoul, Korea. Sooil's U.S. distributor, Dana Diabecare USA LLC, was responsible for conducting the recall actions in the United States and performed the destruction. The insulin pumps were under recall due to a switch malfunction that could cause the insulin pump to not respond when the command key was pressed.

Warning Letter Issued for Failure to File Medical Device Reports

FDA Inspection Discloses Firm's Failure to File Medical Device Reports

On April 9, 2004, FDA's CDRH issued a Warning Letter to Kevin J. O'Neill, President, Pyng Medical Corporation, Richmond, British Columbia V6V 2E9, Canada. During an inspection of Pyng Medical Corporation on November 17 - 20, 2003, an FDA investigator determined that the firm manufactured the F.A.S.T.1 intraosseous infusion system. This product is a device under Section 201(h) of the Act.

The November 2003 inspection revealed that this device was misbranded under Section 502(t)(2) of the Act, in that the firm failed or refused to furnish any material or information as required by Section 519 respecting the device and the Medical Device Reporting (MDR) regulation, 21 CFR Part 803. Significant deviations included, but were not limited to, the following:

- Failure to develop, maintain, and implement proper written MDR procedures, that include a standardized review process/procedure for determining when an event meets the criteria for reporting;

- Failure to submit an MDR within 30 days of receiving or otherwise becoming aware of information that reasonably suggests that a marketed device may have caused or contributed to a death or serious injury. For example, the firm failed to submit MDR reports to the FDA within 30 days for a number of complaints which represented events that should have been reported as serious injuries; and

- Failure to submit an MDR within 30 days of receiving or otherwise becoming aware of information that reasonably suggested that a marketed device malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur.

Seizure of Patient Lift Devices from United States (U.S.) Distributor

Patient Lift Devices Seized Following Injuries And One Patient Death

On June 25, 2004, an FDA investigator accompanied the U.S. Marshals Service in a seizure of approximately 26 Faaborg Patient Lifts, Models PL, VL and Solution/Nordic Series, at Moving Solutions, Inc., in Downers Grove, Illinois. FDA initiated this seizure action because the lifts could break and pose a serious risk to patients. Moving Solutions is the U.S. distributor of the lifts, which are manufactured by Faaborg Rehab Technic Aps, of Denmark.

The patient lifts seized from Moving Solutions, Inc., are mechanical sling-like devices used to lift and move patients from one place to another, as from a bed to a wheelchair. Approximately 850 of these patient lifts had been distributed to hospitals, nursing homes and private homes throughout the U.S.

FDA inspected Moving Solutions on December 2003, January 2004 and March 2004. The inspections found that the firm was the initial importer and distributor of patient lifts and other patient assist devices.

A user facility reported a patient death had occurred on November 23, 2001, associated with the failure of the device. The user facility reported the failure of the bolt that supports the hanger bar that holds the patient sling. As a result, the patient fell and the hanger bar hit the patient on the chest. On January 14, 2004, a second user facility reported that the device failed in the same way causing a serious injury, a hip fracture, to the patient who was being transferred by the device.

The foreign manufacturer's corrective action to address the bolt failure problem was to insert a washer between the hanger bar and the bolt to reduce the wear on the bolt. However, the foreign manufacturer failed to validate or verify that the corrective action would be effective and that the corrective action did not adversely affect the finished device.

In fact, during a May 7, 2004 telephone call, the foreign manufacturer advised FDA that it would take several months to complete the validation process. Moving Solutions recalled

approximately 856 lift devices in distribution by notifying users of the potential for failure and including the washer and installation and repair instructions. This was a Class I recall.

In addition, the FDA inspections found that the domestic firm:

- Failed to report the death and serious injury incidents to FDA and the manufacturer and failed to develop and implement written medical device reporting procedures;
- Failed to report the corrective action to FDA;
- Failed to register its establishment; and
- Failed to implement procedures required by the QS Regulation implemented under 21 U.S.C. 360j(f).

Internet Enforcement

Warning Letter Issued for Colema Boards®

On May 7, 2004, FDA's CDRH issued a Warning Letter to Robert D. Irons, Vice President, Colema Boards of California, Cottonwood, California. The Warning Letter was issued because an FDA review of the firm's web site, http://www.colemaboards.com, revealed a serious regulatory problem involving the product known as "Colema Board®," which is made and marketed by the firm.

Under the Act, this product is considered to be a medical device, because it is used to diagnose or treat a medical condition or to affect the structure or function of the body of man. The law generally requires that manufacturers of medical devices obtain marketing clearance for their products from FDA before they may offer them for sale.

According to the web site, the Colema Board is a home enema kit. An enema kit is a Class I device "intended to instill water or other fluids into the colon through a nozzle inserted into the rectum to promote evacuation of the contents of the lower colon."

However, because the firm was promoting the Colema Board for evacuation of both the lower and upper colon, in addition to other indications the Warning Letter notified the firm that the device was not an "enema kit" and may not be marketed without clearance from FDA. Additionally, the Warning Letter noted that many of the claims on the firm's web site resemble those for a colonic irrigation system, a Class III prescription device.

FDA records did not show that the firm obtained marketing clearance before they began offering the product for sale. The Warning Letter advised the firm that, "The kind of information you need to submit in order to obtain this clearance is described on FDA's device web site at www.fda.gov/cdrh/devadvice. FDA will evaluate this information and decide whether your product may be legally marketed."

Because the firm did not have marketing approval or clearance from FDA, marketing the product is a violation of the law. The Warning Letter advised the firm, "Your product is misbranded under the Act because you did not submit a Section 510(k) premarket notification that shows your device is substantially equivalent to other devices that are legally marketed."

The Warning Letter also noted that, "Colema Board® is also misbranded under Section 502(o) of the Act, in that the device was manufactured, prepared, propagated, compounded, or processed in an establishment not duly registered under Section 510, was not included in a list required by Section 510(j), and a notice or other information respecting the device was not provided as required by Section 510(k)."

The Warning Letter also noted that the firm may be using latex tubing in the manufacture of the device. Devices composed of or containing natural rubber latex must bear the following statement in bold print on the device labeling, "Caution: This Product Contains Natural Rubber Latex Which May Cause Allergic Reactions." FDA regulations require that this statement appear on all device labels, and other labeling, and appear on the principal display panel of the device packaging, the outside package, container or wrapper, and the immediate device package, container, or wrapper. Failure to include this caution misbrands the device under Section 502 of the Act.

In-Vitro Diagnostic Devices

Diagnostic Test Kits Seized

Failure to Correct Violations of the Quality System Regulation Results in Seizure

On February 4, 2004, an FDA investigator accompanied the U.S. Marshal Service in a seizure of various neonatal chemistry and isoelectric focusing diagnostic kits at PerkinElmer Life Sciences, Inc., (PerkinElmer) in Norton, Ohio. The test kits are used to screen for several genetic diseases in newborns and hemoglobin and central nervous system diseases in adults, such as sickle cell anemia and multiple sclerosis.

FDA inspections of the firm revealed the PerkinElmer's devices were adulterated under the Act because they were not manufactured in accordance with FDA's Good Manufacturing Practice Quality System (QS) Regulation.

FDA inspected PerkinElmer's Norton, Ohio, facility on August 21-24, 2001. That inspection revealed numerous violations of the QS Regulation. FDA investigators observed deviations from the QS Regulation that could result in both false positive and negative results. The neonatal tests, the majority of the products sold by this firm, are often used as stand-alone screening tests for disease with major potential impact on patient morbidity and mortality. A false positive result would likely lead to further unnecessary testing and possibly unnecessary treatment.

FDA reinspected PerkinElmer on April 8 - May 16, 2003. That inspection revealed that the firm had not corrected most of the violations observed during the 2001 inspection. It also revealed additional violations in the firm's management control and design control subsystems of the QS Regulation.

FDA inspected PerkinElmer a third time on October 27 - November 5, 2003. The inspection revealed that, while the firm had corrected some of the violations, it had not corrected most of the violations observed during the 2001 and previous 2003 inspections. The inspection revealed two additional violations.

In fact, the firm recalled neonatal total galactose kits in 2004, because of complaints of false positive results. Kits producing false negative results could lead to a failure to diagnose and treat diseases with significant morbidity and mortality.

FDA inspections of PerkinElmer revealed that the firm continually failed to follow the requirements of the QS Regulation when manufacturing in-vitro diagnostic kits. FDA sent PerkinElmer a letter citing these unacceptable practices, giving the company an opportunity to correct the violations, but the company failed to take appropriate corrective actions.

Mammography

Congress passed the Mammography Quality Standards Act of 1992 (MQSA). After passage of MQSA, FDA received authority from the Department of Health and Human Services to implement MQSA.

Facilities that fail accreditation and are not MQSA certified must stop performing mammography. However, once a facility has corrected the problems that caused the failure,

it may apply for reinstatement to reenter the accreditation process. Facility certification can now be extended to include FDA-approved Full Field Digital Mammography (FFDM) units.

FDA qualifies MQSA inspectors who meet specific qualifications and who must maintain this qualification by meeting continuing education and experience requirements. Inspectors receive specialized training in radiation physics, physics related to mammography equipment, and inspecting mammography facilities' compliance with MQSA regulations. All inspectors must pass a series of hands-on tests prior to independently performing inspections.

FDA has classified each adverse inspection into one of three category levels:

- A Level 1 observation indicates a failure to meet a key MQSA requirement that may compromise the quality of mammography performed at the facility;
- A Level 2 observation indicates that the facility meets all key MQSA requirements but fails to meet a significant mammography quality item; and
- A Level 3 observation indicates that the facility meets all major MQSA requirements with only minor problems.

Adverse inspectional observations are placed into a category level based on FDA's assessment of how the observation may affect the quality of mammography. The category level is also used to determine how the facility should respond to the observation. Identical observations found during two consecutive inspections are identified as repeats.

Serious Problems Result in Warning Letter

On September 28, 2004, FDA's New York District Office issued a Warning Letter to Leon Nitkin, M. D., Owner, Metrotech Medical, Inc., Brooklyn, New York. On January 5, 2004, a representative of the State of New York, acting on behalf of FDA inspected the Metrotech Medical, Inc. facility.

No response to that inspection was received by FDA. On March 29, 2004, a follow-up letter was addressed and mailed to Dr. Nitkin at the facility address and once again, no response was received.

An FDA follow-up inspection was conducted on June 21, 2004. This follow-up inspection revealed serious problems involving the conduct of mammography at Metrotech Medical, Inc.

These inspections revealed several violations of MQSA at Metrotech Medical, Inc., which were noted on both of the MQSA Facility Inspection Reports and the document "Important

Information about Your MQSA Inspection ." FDA's investigator mailed this information to Dr. Nitkin's facility on January 5, 2004 and June 28, 2004.

The violations noted during the first inspection of January 5, 2004, are identified below:

- Level 2:

  a) A corrective action was not documented before further exams were taken after Unit #2 had a failing image score, a phantom background optical density, or a density difference outside the allowable regulatory limits;

  b) The medical physicist's survey for x-ray Unit #2 was incomplete because tests were inadequate or not performed.

On June 21, 2004, an FDA representative performed an MQSA follow-up inspection of the facility. This MQSA follow-up inspection revealed that the facility failed to correct the violations identified below:

- Level 1:

  Processor quality control (QC) records in the month of June 2004 were missing for at least 30% of the operating days, for processor unit #1;

  Phantom QC records were missing for at least four weeks for Unit #2.

- Level 2:

  Processor QC records were missing for at least two weeks for processor Unit #1.

- Level 3:

  The screen - film contact QC was not adequate because it was not done at the required frequency.

No Interpreting Physician Available Results in Warning Letter

On August 27, 2004, FDA's San Francisco District Office issued a Warning Letter to Robin Mitchell, Manager, Center for Comprehensive Medicine, Las Vegas, Nevada. On March 23, 2004, a representative of the State of Nevada, acting on behalf of FDA, inspected the Center for Comprehensive Medicine.

Firm Has No System in Place to Provide Timely Lay Summaries to Patients

The Warning Letter listed the following violations of the MQSA that were observed during the inspection:

- Level 1: The system to communicate results was not adequate because there was no system in place to provide timely lay summaries to patients.

- Level 2: There was no designated audit (reviewing) interpreting physician.

- Level 2: The interpreting physician did not meet the continuing experience requirement of having read or interpreted 960 patient examinations in a 24 month period.

- Level 2: The interpreting physician, who had 0 CME credits in 36 months, did not meet the continuing education requirement of having completed a minimum of 15 CME credits in mammography in a 36 month period.

Warning Letter Issued for Level 1 and Level 2 [Repeat] Violations

On August 27, 2004, FDA's San Francisco District issued a Warning Letter to Raju Thiara, Manager, Washington Township Hospital, Fremont, California. On June 28, 2004, a representative of the State of California, acting on behalf of FDA, inspected this facility. The inspection revealed a serious problem involving the conduct of mammography at Washington Township Hospital.

The inspection revealed multiple violations of MQSA related to the performance test that must be conducted on film processors used to develop mammograms:

- Level 1: Processor QC records in the month of August 2003 were missing for 80% of the operating days.

- Level 1: Processor QC records were missing for 25 consecutive days for the hospital processor.

- Level 2: Processor QC records in the month of July 2003 were missing for 18 % of the operating days.

- Level 2: Processor QC records were missing for 3 consecutive days for the outpatient clinic.

- Level 2 (REPEAT): Mammograms were processed in a film processor when it was out of limits on 4 days.

- Level 2 (REPEAT): Corrective actions for processor QC failures were not documented at least once.

FDA Files Administrative Complaint for Civil Money Penalties Against Ecumed Health Group; Notifies Patients of Mammography Problems

FDA Determines Mammogram Reviews are of Poor Quality and Not Reliable

On July 19, 2004, FDA filed an Administrative Complaint for Civil Money Penalties against the Ecumed Health Group Facility, Hialeah, Florida. FDA's review of a sample of mammography examinations done by the Ecumed Health Group facility showed that the mammograms were of poor quality and not reliable and the facility did not meet the standards for clinical image quality as required by FDA. Under MQSA, FDA's role is to ensure that all mammography facilities meet certain high quality standards.

On August 23, 2004, FDA announced that the Agency was alerting patients about possible problems associated with the quality of mammograms performed at the Ecumed Health Group Facility in Hialeah, Florida, after January 7, 2001. The facility stopped performing mammograms.

FDA worked closely with Florida's Bureau of Radiation Control to inspect the facility and develop information about the nature and extent of the problems there. As a result, Florida's Bureau of Radiation Control withdrew the facility's authorization to use the mammography unit and fined the facility for operating the unit without proper state authorization. FDA is also pursuing fines against the facility.

While this information does not necessarily mean that the results of all of the examinations are inaccurate, it does mean that patients might need to have mammograms re-evaluated and possibly repeated.

FDA contacted all physicians' offices known by the Agency to have sent mammography patients to the Ecumed Health Group Facility and informed them of the problem. Physicians who were not contacted by FDA were asked to contact the Ecumed Health Group Facility for further patient information if they believed that that one or more of their patients had a mammogram at this facility during the time period in question.

FDA provided the following advice for patients: 1)Patients who have had a mammogram at another facility since the one taken at the Ecumed Health Group Facility need not take any action other than to follow the recommendations from the subsequent mammogram; and 2) Patients who had a mammogram at the Ecumed Health Group Facility any time after January 7, 2001, and have not had a mammogram at another facility since then, should have their mammogram re-evaluated or repeated.

Civil Money Penalty for Mammography Facility

Facility Fined for Performing Mammograms Without a Certificate

Korangy Radiology Associates, P.A., et al. On May 27, 2004, the Honorable Daniel J. Davidson granted CDRH's motion for partial summary judgment on the issue of liability in a civil money penalty action for violations of MQSA. Judge Davidson found that Respondents Amile A. Korangy, M.D. and Korangy Radiology Associates, P.A., t/a Baltimore Imaging Centers, were each liable for 193 violations of MQSA: 1 each for failing to obtain a certificate to perform mammography services; and 192 each for mammograms performed without a certificate.

In so finding, Judge Davidson held that there was no genuine issue of material fact as to whether Respondents violated MQSA because their prior mammography certificate contained notice on its face that it had expired, and Respondents nevertheless continued to perform mammography services without a new certificate.

OB/GYN, Gastrointestinal and Urology Devices Branch

Warning Letter Issued for Gynecare Intergel Adhesion Prevention Solution

On October 8, 2004, FDA's CDRH issued a Warning Letter to Dennis J. Allingham, President and CEO, Lifecore Biomedical, Inc., Chaska, Minnesota. The Warning Letter was issued because a FDA inspection in April - May 2004, revealed a serious regulatory problem involving the product known as Gynecare Intergel Adhesion Prevention Solution (INTERGEL), which is manufactured by the firm.

Under the Act, this product is considered to be a medical device. The inspection revealed that Intergel is misbranded under section 502 (t) (2) of the Act in that the firm failed to furnish material or information as required under section 519 of the Act and regulations implementing that section at Title 21, *Code of Federal Regulations,* Part 803 – Medical Device Reporting (MDR).

Warning Letter Issued for Sea Tangle Laminaria Tents (Cervical Dilators)

On August 3, 2004, FDA's CDRH issued a Warning Letter to Johan Gjemre Olsen, CEO/Leader of the Board, Ola Olsen Eftf. A/S, Stavanger, Norway. The Warning Letter was issued because a FDA inspection in March 2004, revealed serious regulatory problems involving the product known as Sea Tangle Laminaria Tents (cervical dilators), which are manufactured by the firm.

Under the Act, this product is considered to be a medical device. The inspection revealed that the devices are adulterated within the meaning of section 201(h) of the Act in that methods used in, or the facilities or controls used for, their manufacturer, packing, storage, or installation are not in conformity with applicable Current Good Manufacturing Practice (CGMP) requirements, which re set for in FDA's Quality System (QS) regulation, codified at Title 21, *Code of Federal Regulations,* Part 820. The firm is included in Import Alert #89-04 to prevent importation of the subject devices.

Ophthalmology

FDA Again Warns Consumers of the Dangers of Using Decorative Contact Lenses Without Proper Professional Involvement

FDA Received Reports of Corneal Ulcers From Use of Decorative Contact Lenses

On October 28, 2004, FDA again issued a warning to consumers during the Halloween season about serious risks of using decorative contact lenses distributed without appropriate involvement from an eye care professional. These decorative lenses can cause permanent eye injury and may potentially lead to blindness.

FDA received reports of decorative contact lenses being marketed and distributed directly to consumers through sources such as flea markets, convenience stores, beach shops and the Internet.

FDA received reports of corneal ulcers associated with the wearing of decorative contact lenses in excess of the recommended period. Corneal ulcers can progress rapidly, and, if left untreated, could lead to infection of the eye. Uncontrolled infection can lead to corneal scarring and vision impairment. In the most severe cases, this condition can result in blindness and eye loss.

Other risks associated with the use of decorative contact lenses include conjunctivitis (an infection of the eye), corneal edema (swelling), an allergic reaction, and corneal abrasion due to poorly fit lens. Other problems may include a reduction in visual acuity (sight), contrast sensitivity, and other visual functions resulting in interference with driving and other activities.

"Consumers should understand that decorative contact lenses, like contact lenses intended for correcting vision, present serious risks to eye health if they are distributed without the appropriate involvement of a qualified eye care professional," said Dr. Lester M. Crawford, Acting FDA Commissioner. "FDA will aggressively use the full range of its statutory authorities to prevent the improper distribution of these potentially dangerous products."

FDA has issued an import alert for decorative contact lenses presented for importation into the U. S. that are intended for distribution without the appropriate involvement of an eye care professional.

The Agency examined numerous entries of decorative contact lenses presented for importation. Currently, there has been no demonstration to FDA's satisfaction that these products, when distributed without eye care professional involvement, comply with federal safety standards. Consequently, these products have not been permitted to enter U. S. commerce.

Domestically, FDA inspected several firms distributing decorative contact lenses. FDA has issued several Warning Letters to firms that were selling decorative contact lenses without proper labeling about the risks and proper instructions for safe use. FDA stated that it will take action with respect to other firms distributing these products as appropriate.

FDA has sent letters to Yahoo and the on-line auction site eBay, alerting them to the risks of decorative contact lenses distributed without appropriate eye care professional involvement and requesting their assistance in preventing improper online sales.

The Agency has also worked with the Florida Department of Health to have "stop sale" orders issued to two retail establishments selling decorative contact lenses without the involvement of an eye care professional. FDA is investigating several potential sources of decorative lenses, and will pursue enforcement action against prescription contact lenses being diverted to OTC sale as appropriate. FDA continues to work with State authorities to address contact lens diversions.

FDA urges consumers not to use decorative contact lenses unless they have seen an eye care professional and have obtained proper fitting and instructions for using the product. FDA requests that consumers report any complaints to FDA's District Office consumer complaint coordinator in their geographic area.

Warning Letter Issued to Manufacturer of Soft Contact Lenses

FDA Inspection Reveals CGMP Violations of the Quality System Regulation

On April 23, 2004, FDA's CDRH issued a Warning Letter to Mr. Gun Ho Bea, Chief Executive Officer of Bescon Co., Ltd., Chunan-City, Chungham, Korea. During an inspection of the firm in November 2003, an FDA investigator determined that the firm manufactured daily wear soft contact lenses. These products are devices as defined by Section 201(h) of the Act.

The above-stated inspection revealed that these devices were adulterated under Section 501(h) of the Act, in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation were not in conformance with CGMP requirements of the QS Regulation. Significant deviations included, but were not limited to, the following:

- Failure to adequately validate the process used to sterilize the lenses;
- Failure to establish and maintain adequate acceptance procedures, which include inspections, tests, or other verification activities, to ensure that specified requirements for the firm's devices are met. In addition, there was a failure to document acceptance activities to include the activities performed, the dates the activities were performed, the results and the signature of the person conducting the activities; and

- Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specification.

The Warning Letter further stated that given the serious nature of these violations of the Act, all devices manufactured by Bescon Co., Ltd., Chunan-City, Chungham, Korea, may be detained without physical examination (DWPE) upon entry into the U.S. until these violations are corrected. The Warning Letter advised that in order to prevent the devices from being DWPE, the firm will need to respond to the Warning Letter and correct the violations noted in the Warning Letter.

In addition, the Agency usually needs to conduct a follow-up inspection to verify that appropriate corrections have been implemented. Bescon has since adequately responded in writing to the Warning Letter. A follow-up inspection was also conducted December 2004 and deemed to be acceptable.

Orthopedics

Warning Letter Issued to Synthes for Marketing of a Bone Void Filler for Vertebroplasty and other MDR and GMP Violations

FDA Issues *For Cause* Inspection Following Reports of Three Patient Deaths Associated with Norian XR Device

On November 5, 2004, The Center for Devices and Radiological Health (CDRH) issued a Warning Letter to Synthes Inc. located in West Chester, Pennsylvania. CDRH issued a *for cause* inspection request for Synthes USA and Norian Corporation after receiving a report of three patient deaths associated with the use of the Norian XR device in vertebroplasty and kyphoplasty procedures. Norian XR is a calcium phosphate bone-void filling material manufactured by Norian and distributed by Synthes Spine of West Chester, Pennsylvania. The information received by CDRH suggested that the company conducted a clinical study without an approved Investigational Device Exemption (IDE) and promoted use of the Norian XR device for uses that had not been cleared via a 510(k) or approved via a PMA.

Based on the evidence collected during the inspection, FDA concluded that the firm was promoting Norian XR for vertebroplasty and kyphoplasty which constituted significant modifications to the intended uses of Norian XR. Norian® XR Calcium Phosphate Bone Void Filler is intended only for bony voids or defects that are not intrinsic to the stability of the bony structure. Evidence collected during the inspection also revealed that the firm was collecting safety and effectiveness data regarding the use of Norian XR for vertebroplasty and kyphoplasty procedures. The Warning Letter notes that the collection of this data

constituted a study conducted to determine the safety and effectiveness of using the Norian XR in a manner not cleared by FDA, requiring an FDA-approved IDE. The Warning Letter concludes that the Norian XR device is adulterated and misbranded because the firm's promotion of the Norian XR and introduction of the device into interstate commerce for new intended uses.

Additional MDR and QS violations were also noted during the inspection. The inspection revealed that Norian XR and Norian SRS are misbranded because the firm failed to submit information to the FDA as required by the Medical Device Reporting (MDR) regulations. The following violations were noted in the Warning Letter:

1. The firm failed to submit an MDR report within thirty days of becoming aware of a patient death on January 13, 2003.

2. The firm failed to report supplemental information as required by 21 CFR 803.56, which provides that when "a manufacturer obtains information required under this part that was not provided because it was not known or was not available when the initial report was submitted, the manufacturer shall submit to FDA the supplemental information within 1 month."

3. The firm failed to include in their MDR event files information in their possession or references to information related to the adverse event and all documentation of their deliberations and decision making processes used to determine if a device-related death, serious injury, or malfunction was or was not reportable.

The inspection also revealed that the firm's medical devices appear to be adulterated in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the Current Good Manufacturing Practice (CGMP) requirements of the Quality System (QS) regulation found at 21 CFR Part 820. The following violations were noted in the Warning Letter:

- Failure to maintain procedures for receiving, reviewing, and evaluating complaints by the formally designated complaint unit.

Surgical

Warning Letter Issued for Failure to File MDRs

Warning Letter Details Over 17 Complaints That Were Not Reported Under MDR Regulation

On February 24, 2004, FDA's Denver District Office issued a Warning Letter to Dr. Robert W. Christensen, President/CEO of TMJ Implants, Inc., Golden, Colorado. FDA investigators conducted an inspection of the firm between July 29, 2003 and August 11, 2003. This inspection determined that TMJ Implants, Inc., manufactures fossa eminence prostheses, condyle prostheses and related items for temporomandibular joint (TMJ) implantation.

The inspection revealed that the firm's devices are misbranded under Section 502(t)(2) of the Act in that the firm failed or refused to furnish information to FDA as required by the MDR Regulation. Specifically, the firm failed to submit MDR reports to FDA after receiving information which reasonably suggested that one of the commercially distributed devices may have caused or contributed to a death or serious injury.

The Warning Letter stated that a number of events in the firm's complaint system reasonably suggested that one of the firm's distributed devices may have caused or contributed to a death or serious injury or had malfunctioned and such device or similar device marketed by the firm would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur. The Warning Letter detailed over 17 complaints that were reportable and should have been reported as serious injury MDRs. For example, four MedWatch reports were combined into one complaint by the firm. The Warning Letter noted, "These MedWatch reports should have been submitted as four individual serious injury MDRs."

The following is one example of a complaint that was not reported as required by the MDR Regulation:

> "Information in the complaint indicates that bilateral total prostheses were removed in order to clear up an infection and perforation between the external auditory canal and joint space. At operation, the screws in the condylar portion were all loose except for the inferior two screws, which were marginally tight. One of the screws was completely lifted out of its hole in the condylar portion of the prosthesis. The tissue showed moderate acute and chronic inflammation and fibrinoid necrosis. This event is reportable as a serious injury MDR."

Tissues

American Red Cross Transplantation Services Receives Warning Letter

On March 11, 2004, FDA's Los Angeles District Office issued a Warning Letter to Mark

Johnson, Tissue Processing Group Manager, American Red Cross Transplantation Services (ARCTS), Costa Mesa, California. FDA conducted an inspection of this firm between October 20 and November 25, 2003. FDA investigators determined that the firm manufactures and distributes cryopreserved heart valves, which are regulated as devices, and human tissues for transplantation, which are regulated as tissues under 21 CFR Part 1270 and Section 361 of the U.S. Public Health Service Act.

C*ryopreserved Human Heart Valve Allograft*

The cryopreserved human heart valve allograft is a device as defined by Section 201(h) of the Act. FDA investigators documented significant deviations from the QS Regulation, which cause these devices to be adulterated. These deviations included the following:

- Failure of management to fully implement and maintain an adequate and effective Quality System and Quality Policy at all levels of the organization;
  Failure to establish and maintain a design history file for the human heart valve allograft device, a Class III device, containing or referencing the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of this part;

- Failure to ensure that device packaging and shipping containers are designed and constructed to protect the device from alteration or damage during the customary conditions of processing, storage, handling, and distribution;
- Failure to perform adequate process validation with a high degree of assurance;
  Failure to establish a Device Master Record in that the Device Master Record does not contain or refer to the location of device specifications and packaging and labeling specifications;
  Failure to establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements; and
  Failure to establish and maintain procedures for acceptance of incoming product.

Human Tissue Intended for Transplantation

FDA investigators also determined that ARCTS processes human tissue intended for transplantation. FDA investigators documented significant violations of the requirements for this human tissue. These violations included the failure to prepare, validate, and follow written procedures for the prevention of infectious disease contamination and cross-contamination during processing.

Unapproved Devices

Warning Letter Issued for Revitalite Beautifying Soft Light Laser

On March 25, 2004, FDA's CDRH issued a Warning Letter to Mr. George MacDonald, President, Anti Aging Solutions, Inc., Toronto, Ontario, Canada. The Warning Letter stated that on December 31, 2003, FDA's Buffalo District Office had detained a shipment of Revitalite Beautifying Soft Light Laser (Revitalite), which is marketed by Anti Aging Solutions, Inc. The Warning Letter advised that while the firm had submitted a 510(k) premarket notification for Revitalite, FDA had not cleared the product for sale in the U.S.

Under Section 201(h) of the Act, an instrument is considered a medical device if it is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of diseases, or because it is intended to affect the structure or any function of the body. According to the information the firm submitted with the Section 510(k) premarket notification, Revitalite is a low level laser intended for the treatment of chronic neck and shoulder pain of musculoskeletal origin. Revitalite is therefore a medical device.

FDA further stated in the Warning Letter that FDA records showed that the firm did not obtain marketing clearance or approval before they began offering Revitalite for sale. Marketing this product in the U.S. without clearance or approval from FDA is a violation of the law.